

Amendments to the Claims

Applicants amend claims 1 and 72. Claims 1-4, 7-13, 15-26, 29-32, 34-44, 47-50, 72 and 287-310 remain pending upon entry of this amendment. Amendments to the claims are provided in the below listing of claims.

Listing of Claims

1. (currently amended) A device for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, which device comprises:

a non-conductive substrate;

a plurality of electrode arrays positioned on said substrate, wherein each electrode array comprises at least two electrode structures positioned on the same plane and having substantially the same surface area, and further wherein each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 and 15 times the width of the electrode gap between electrode elements of different electrode structures within said each electrode array, further wherein the electrode gap is at least 3 microns wide;

a plurality of connection pads located on said substrate, wherein each connection pad is in electrical communication with at least one of said electrode structures;
and

wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth results in cellular contact with at least one of said electrode structures further resulting in a detectable change in AC electrical impedance between or among said electrode structures.

2. (original) The device according to Claim 1, wherein the substrate comprises glass, sapphire, silicon dioxide on silicon, or a polymer.

3. (original) The device according to Claim 2, wherein the substrate is configured as a flat surface.

4. (original) The device according to Claim 3, further comprising a plurality of receptacles, wherein each receptacle is disposed on the nonconductive substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid tight container and least one container is associated with an electrode array on the substrate.

5. (CANCELED)

6. (CANCELED)

7. (previously presented) The device according to Claim 1, wherein the electrode elements of each electrode structure are of equal widths.

8. (previously presented) The device according to Claim 1 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are between about 0.5 times and about 10 times the size of cells used.

9. (previously presented) The device according to Claim 1, wherein electrode elements' widths are in the range between 20 micron and 500 micron.

10. (previously presented) The device according to Claim 1, wherein the at least two electrode elements comprise a plurality of electrode elements, further wherein the plurality of electrode elements of different electrode structures are evenly spaced.

11. (previously presented) The device according to Claim 1, wherein each array of electrodes is organized in an interdigitated fashion.

12. (previously presented) The device according to Claim 1, wherein each array of electrodes is organized so that electrode elements have a geometry selected from the group consisting of circle-on-line, diamond-on-line, concentric, sinusoidal, interdigitated or castellated fashion.

13. (previously presented) The device according to Claim 10, further wherein at least one bus is associated with up to half of the plurality of electrode elements in the at least two electrode structures of each electrode array.

14. (CANCELED)

15. (original) The device according to Claim 13, wherein the bus comprises an electrode which extends around up to half the perimeter of the electrode array.

16. (previously presented) The device according to Claim 13, further comprising a plurality of receptacles, wherein each receptacle is disposed on the nonconductive substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container and each electrode array on the substrate is associated with a fluid-tight container.

17. (original) The device according to Claim 16, wherein each container is shaped as a tube with opposing open ends, one end of which being in fluid-tight contact with the substrate.

18. (original) The device according to Claim 17, further wherein the diameter of the container at the end in contact with the substrate is smaller than the diameter of the opposing end.

19. (previously presented) The device according to Claim 16, wherein the containers are arranged on the substrate in honeycomb fashion.

20. (original) The device according to Claim 19, wherein the outer wall of each container at its point of contact with the substrate is up to about 2.5 mm from the outer wall of each adjacent container.

21. (previously presented) The device according to Claim 19, wherein the electrode elements of each electrode array are of equal widths.

22. (previously presented) The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are between about 0.5 times and about 10 times the size of cells used.

23. (previously presented) The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are in the range between 20 micron and 500 micron.

24. (previously presented) The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of the electrode structures ranges from 0.2 time and 3 times the width of an averaged cell used.

25. (previously presented) The device according to Claim 1, further comprising an impedance analyzer electrically connected to all or a plurality of the electrical connection pads.

26. (original) The device according to Claim 25, wherein the impedance is measured at a frequency ranging from about 1 Hz to about 1 MHz.

27. (CANCELED)

28. (CANCELED)

29. (original) The device according to Claim 19, wherein the containers together form a multi-well bottomless microtiter plate.

30. (original) The device according to Claim 29, wherein the number of wells present in the bottomless microtiter plate is a number between 6 and 1,536.

31. (previously presented) The device according to Claim 19, wherein less than all of the containers are associated with at least one of said plurality of electrode arrays.

32. (previously presented) The device according to Claim 30, wherein less than all of the containers are associated with at least one of said plurality of electrode arrays.

33. (CANCELED)

34. (original) The device according to Claim 19, wherein the diameter of one or more containers is, at the container end disposed on the substrate, between about 3 and 7 mm.

35. (original) The device according to Claim 1, wherein the electrodes are fabricated on the substrate by a laser ablation process.

36. (previously presented) The device according to Claim 1, wherein the electrode arrays are individually addressed.

37. (previously presented) The device according to Claim 1, further comprising: one or more capture reagents immobilized on the surfaces of the at least two electrode structures in each electrode array, wherein the capture reagents are capable of binding target cells.

38. (previously presented) A method for assaying target cells in a sample, which method comprises:

- a) contacting one or more electrode arrays of the device of Claim 1 to a sample containing or suspected of containing target cells; and,
- b) determining whether a change in impedance occurs between or among electrode structures in one or more said electrode arrays;

wherein a detectable change of impedance is indicative of the presence of target cells in said sample, and attachment of said cells on the surface of said one or more electrode arrays.

39. (original) The method according to Claim 38, wherein the sample is a biological sample comprising culture media sufficient for target cell growth.

40. (previously presented) The device according to Claim 1, further comprising: an impedance analyzer and connection means for establishing electrical communication between the connection pads and the impedance analyzer.

41. (original) The device according to Claim 40, wherein the connection means comprises a mechanical clip adapted to securely engage the substrate and to form electrical contact with a trace.

42. (original) The device according to claim 41, wherein the mechanical clip is adapted to form an electrical connection with a printed-circuit board (PCB).

43. (previously presented) The device according to Claim 1, wherein the target cells are attached on an electrode surface.

44. (original) The device according to Claim 4, wherein a perimeter of the container is contained within the outer perimeter of the electrode arrays.

45. (CANCELED)

46. (CANCELED)

47. (original) The device according to Claim 13, further comprising a plurality of receptacles, wherein each receptacle is disposed on the substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container, and at least one receptacle is contained within a perimeter formed by the buses at a plane of contact between the receptacles and the substrate.

48. (previously presented) The device according to Claim 47, wherein each container is shaped as a tube with opposing open ends, one end of which being in fluid-tight contact with the substrate.

49. (original) The device according to Claim 48, wherein the diameter of the container at the end in contact with the substrate is smaller than the diameter of the opposing end.

50. (original) The device according to Claim 47, wherein the containers are arranged on the substrate in honeycomb fashion.

51 – 71 (canceled)

72. (currently amended) A device for monitoring cell-substrate impedance, which device comprises:

- a) a non-conducting substrate;
- b) at least two electrode structures fabricated to the same side of said substrate, wherein:
 - i) each of said at least two electrode structures has at least two electrode elements; and
 - ii) said at least two electrode structures have substantially same surface area;
 - iii) said electrode elements and gaps between said electrode elements of different electrode structures are arranged so that there is a more than 50% probability for cells to contact an electrode element when said cells are introduced onto said device, wherein each of the gaps is at least 3 microns wide; and
- c) at least two connection pads located on said substrate,

wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on any of said at least two electrode structures results in detectable change in AC electrical impedance between or among said electrode structures.

73 – 286 (canceled)

287. (previously presented) The device according to Claim 1 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of electrode structures ranges from 0.2 time and 3 times the width of an averaged cell used.

288. (previously presented) The device according to Claim 1 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of the electrode structures is between about 3 microns and 80 microns.

289. (previously presented) The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of the electrode structures is between about 3 microns and 80 microns.

290 (previously presented) The device according to Claim 7, wherein the electrode elements' widths are between about 0.5 times and about 10 times the size of cells used.

291. (previously presented) The device according to Claim 7, wherein the electrode elements' widths are in the range between 20 micron and 500 micron.

292. (previously presented) The device according to Claim 7, wherein the gap between electrode elements of different electrode structures ranges from 0.2 time and 3 times the width of an average cell used.

293. (previously presented) The device according to Claim 7, wherein the gap between electrode elements of different electrode structures is between about 3 microns and 80 microns.

294. (previously presented) The device according to Claim 1, wherein the electrode structures comprise one or more materials selected from the group consisting of indium tin oxide (ITO), chromium, gold, copper, nickel, platinum, silver, titanium, steel, and aluminum.

295. (previously presented) The device according to Claim 1, wherein the electrode structures are optically transparent.

296. (previously presented) The device according to Claim 1, wherein the surface of the electrode structures are modified with a cell-adhesion promotion moiety.

297. (previously presented) The device according to Claim 296, wherein the cell-adhesion promotion moiety is selected from the group consisting of a self-assembly-monomolecular (SAM) layer, one or more extracellular matrix components, a protein, a polymer layer and a charged group.

298. (previously presented) A method for monitoring cell attachment or growth, which method comprises:

- a) providing the device of Claim 16;
- b) attaching cells to or growing cells on the surface suitable for attachment or growth; and
- c) monitoring a change of impedance between or among the electrode structures to monitor said cell attachment or growth.

299. (previously presented) The method according to Claim 298, further comprising determining the amount or number of cells that are attached to or grown on the device from the monitored impedance.

300. (previously presented) The method according to Claim 298, further comprising deriving a cell number index from the monitored impedance.

301. (previously presented) The method according to Claim 300, wherein the cell number index is derived from a process selected from the group consisting of process 1, process 2, process 3 and process 4,

wherein process 1 comprises:

- a) at each measured frequency, calculating a resistance ratio by dividing a measured resistance when cells are attached to the electrode structure by a baseline resistance;
- b) determining the maximum value in the resistance ratio over a frequency spectrum; and

- c) subtracting one from the maximum value in the resistance ratio, wherein a zero or near zero cell number index indicates that no cells or a very small number of cells are present on or attached to the electrode structures and an increased value of cell number index indicates that, for the same type of cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures;

wherein process 2 comprises:

- a) at each measured frequency, calculating the resistance ratio by dividing a measured resistance when cells are attached to the electrode structures by the baseline resistance;
- b) determining the maximum value in the resistance ratio over a frequency spectrum; and
- c) calculating a log-value of the maximum value in the resistance ratio;

wherein, a zero or near-zero cell number index indicates that no cells or a very small number of cells are present on or attached to the electrode structures and an increased value of cell number index indicates that, for same type of the cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures;

wherein process 3 comprises:

- a) at each measured frequency, calculating the reactance ratio by dividing the measured reactance when cells are attached to the electrode structures by the baseline reactance;
- b) determining the maximum value in the reactance ratio over a frequency spectrum; and
- c) subtracting one from the maximum value in the resistance ratio,

wherein a zero or near-zero cell number index indicates that no cells or a very small number of cells are present on or attached to the electrode structures and an increased value of cell number index indicates that, for same type of the cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures;

and wherein process 4 comprises:

- a) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrode structures by the baseline resistance;
- b) calculating the relative change in resistance in each measured frequency by subtracting one from the resistance ratio; and
- c) integrating all the relative-change values;

wherein the cell-number index is derived based on multiple-frequency points, and further wherein a zero or near-zero cell number index indicates that no cells or a very small number of cells are present on the electrodes and an increased value of cell number index indicates that, for same type of the cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures.

302. (previously presented) The method according to Claim 298, wherein the cell attachment or growth is monitored on a real time basis.

303. (previously presented) The method according to Claim 298, wherein the cell attachment or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates attachment or growth of the cells.

304. (previously presented) The method according to Claim 298, wherein the cell attachment or growth is stimulated by a growth factor and the method is used to screen the test compound for a growth factor antagonist.

305. (previously presented) A method for monitoring effect of a test compound on cell attachment or growth, which method comprises:

- a) providing a device of Claim 16;
- b) attaching cells to or growing cells in a plurality of containers of said device wherein each of said plurality of containers is associated with at least two electrode structures and contains substantially the same number and same type of cells and a different concentration of a test compound; and
- c) monitoring a change of impedance between or among the electrode structures as a function of time to monitor the effect of said test compound on cell attachment or growth.

306. (previously presented) The method according to Claim 305, further comprising determining whether the test compound is an antagonist to the growth of the cells.

307. (previously presented) The method according to Claim 305, further comprising determining the dose response of the test compound.

308. (previously presented) A method for electroporating adherent cells, which method comprises:

- a) providing a device of Claim 16 comprising a plurality of containers, at least one of said containers comprising at least two electrode structures;
- b) attaching or growing cells in said at least one of said containers; and
- c) applying electrical voltage pulses to said electrode-structures to electroporate the membrane of said cells adhered to the bottom surface of said electrode structures of said at least one of said containers.

309. (previously presented) The device according to Claim 72 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are between about 0.5 times and about 10 times the size of cells used.

310. (previously presented) The device according to Claim 72 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of the electrode structures ranges from 0.2 time and 3 times the width of an averaged cell used.